METASTATIC CALCIFICATION ASSOCIATED WITH HYPERVITAMINOSIS D AND HALIPHAGIA *

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The occurrence of metastatic calcification with various types of osseous lesions [1-5] and with chronic renal disease [6] in human pathology is well known. Experimentally, the feeding of calcium salts,[7,8] the administration of large doses of vitamin D,[9-11] and the injection of great amounts of parathyroid hormone [12,13] have also resulted in metastatic calcification. From the point of view of human pathology the rôle of vitamin D in the production of this lesion rests on rather scanty evidence.[14-17]

HUMAN CASES OF HYPERVITAMINOSIS D FROM THE LITERATURE

Putschar [14] observed a male infant, 5½ months old, who received vigantol (irradiated ergosterol) for about 3 months before death. Autopsy disclosed emaciation, small adrenal glands, moderate fatty metamorphosis of the liver, a peculiar lipogranulomatous reaction in the hypodermis, and calcium deposits in the kidneys. These deposits involved mainly the epithelial cells, lumina, and basement membranes of the distal convoluted tubules, and also the stroma adjacent to them. The collecting tubules and the surrounding stroma in the pyramids were similarly involved and in much greater degree. No reactive or regressive changes were present near the calcium deposits.

Thatcher [15] reported the case of a male infant, 18 months old, who received irradiated ergosterol for 9 months before death. At autopsy the kidneys were enlarged, firm, and pale yellow. The medulla at the bases of the pyramids showed tiny, gritty, gray particles which microscopically were masses of calcium lying mainly in the lumina of the collecting tubules at the corticomedullary junction, with calcification of some adjacent epithelial lining cells. Calcified cells were identified in the masses of calcium, some of which were encircled by cellular fibrous tissue. The segments of tubules proximal to the calcium masses were dilated. Calcium was not found in other organs. The liver showed extensive fatty metamorphosis.

Thatcher [16] reported a second case in a male infant, 11½ months old, who had received much solar irradiation, two ultraviolet ray treatments, and a large amount of cod-liver oil for 4 months. Necropsy findings were practically identical with those in his first case.

Gissel and Bufe [17] administered large doses of dihydrotachysterol

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to two infants with meningomyelocele and hydrocephalus. One died at the age of 128 days. In addition to ascending meningitis and pyocephalus found at autopsy, the kidneys showed heavy calcium deposits in the epithelium of the cortical and medullary tubules as well as calcium casts in their lumina and scattered, finely granular calcium incrustations in the neighboring interstitial tissue. The second infant died of ascending meningitis and internal pyocephalus at the age of 54 days. The kidneys showed detached calcium casts in the cortical portions of the collecting tubules with absent or newly regenerated epithelial cells adjacent. The lungs, heart, liver, spleen, and stomach in both cases showed no calcium deposits.

Wells and Holley [5] thought that the reasons for metastatic calcification in the lungs, left atrial endocardium, kidneys, gastric mucosa, and hypodermis in their case of osteitis deformans were the easier mobilization of calcium from the bones in this disease, and the massive doses of viosterol given to the patient.

The observation of a recent case of metastatic calcification, in which the patient ingested vitamin D and several inorganic salts, furnishes provoking problems for solution.

Report of Case

A cab driver, 44 years old, born in Scotland, was admitted to St. Luke's Hospital in Denver under the care of Dr. C. R. Cooper, who kindly gave permission for use of the clinical details. Since the patient was comatose, the history was obtained from his wife, who stated that for about 6 months before admission and for little understood reasons he had been taking daily doses of a vitamin D preparation as well as liberal amounts of a mildly laxative compound containing sodium sulfate, sodium bicarbonate, sodium phosphate, and sodium chloride. His wife warned him repeatedly that this was a hazardous procedure without the advice of a physician, but he persisted in his autotherapy. Two weeks before admission he had suffered from malaise, weakness, restlessness, and drowsiness. One week before he had seen an osteopath who diagnosed Bright's disease and prescribed some unknown medication. Since he did not improve and experienced periods of stupor alternating with bouts of delirium, he was admitted to the hospital on July 2, 1944, at 11:35 A.M. His temperature was 99.8° F. and his pulse was 90 beats per minute. His respirations were labored and numbered 26 per minute. Physical examination revealed stupor, pallor, a loud, blowing, systolic murmur over the entire precordium, lungs clear to percussion and auscultation, and no significant changes in the abdomen except for a healed appendectomy scar. The voided urine was amber, murky, and acid. The specific gravity was 1.022, albumin was 3 plus, and sugar and acetone were absent. Microscopic examination disclosed many granular casts, an occasional leukocyte, and 20 to 30 erythrocytes per low-power field. A roentgenogram of the chest showed a diffuse fine mottling throughout both lungs with some hilar mottling. This appearance was interpreted as pulmonary edema. Blood counts and chemical determinations were not obtained. At 4:00 P.M., when 500 cc. of plasma and 1000 cc. of normal saline solution were injected intravenously, the pulse was rapid, irregular, and difficult to count. At 7:00 P.M. the patient was expectorating thick, yellow sputum, his breathing was stertorous and rapid, and he moved restlessly

in bed, although in coma. His pulse was 140 and his temperature was 98° F. At 1:30 A.M. on July 3rd, he died.

AUTOPSY FINDINGS

At autopsy, 8 hours after death, the body weighed 160 lbs. (78 kg.) and measured 72 inches (183 cm.) long. Externally, the only significant finding was a healed appendectomy scar. The panniculus adiposus was 3 cm. thick and the skeletal muscles were well developed and dark red. The peritoneal surface was smooth and moist except for adhesions of the omentum and the cecum to the under surface of the laparotomy scar. The pleural cavities and the pericardial sac were normal. The thymus was small and consisted of soft, yellow tissue. The thyroid gland *in situ* was normal in size, firm, gray-red, and finely lobulated. No tumors were found near the thyroid gland, although the parathyroid glands were not examined specifically.

The heart weighed 480 gm. and the epicardial fat was abundant. The myocardium was firm and gray-red. The right ventricle was 3 to 5 mm. and the left ventricle 16 to 20 mm. thick. A gray-red clot adhered to the lining of the left auricular appendage. The foramen ovale was closed. The valve leaflets were all thin and translucent. The valve circumferences were as follows: tricuspid, 12 cm.; pulmonic, 6.8 cm.; mitral, 10 cm.; and aortic, 6.5 cm. The coronary arteries were patent and their elasticity was moderately reduced. The first portions of the main branches showed irregular, yellow, intimal thickening. The aorta was moderately elastic and of usual caliber. A few pin-point, yellow dots marked the intima at the root and fine, yellow, longitudinal streakings were lightly scattered in the intima of the abdominal segment. The stems of the great vessels were patent.

The right lung weighed 780 gm.; the left lung, 810 gm. The surfaces were smooth and the lobes were discrete. Except for the apices and anterior margins, both lungs were subcrepitant on sectioning, dark red, finely black-streaked, and oozed plentiful foamy gray fluid. The trachea and bronchi had intact mucosa and a fairly abundant content of pale yellow mucoid material. The pulmonary arteries were normal. The mediastinal lymph nodes were small, soft, black and gray mottled.

The spleen weighed 420 gm. Visible through the thin capsule and extending down into the firm, flat, gray-red parenchyma were four dark purple, map-like areas, 1.5 to 4 cm. in greatest diameters.

The esophagus was normal. The stomach contained a scant amount of yellow, thin fluid and was lined by a reddened, well folded, intact mucosa. The small intestine contained similar fluid. The appendix was absent. The colon contained soft, well formed, dark brown feces.

The liver weighed 2,280 gm. The capsule was thin. The cut section was firm, tan, and focally marked by pale yellow areas, 6 to 12 mm. in diameter. The biliary ducts and blood vessels were well preserved. The gallbladder had a smooth serosa, a fairly thin wall, a dark green mucosa, and contained one large, oval stone measuring 4.5 by 3.5 by 2.5 cm., which was rough, tan and dark green, and six dark green, faceted calculi measuring 5 to 6 mm. in diameter. The bile was thick and dark green. The pancreas was normal in size, firm, tan, and coarsely lobulated.

The cortices of the large adrenal glands were fairly thick. The medulla of the right was entirely, and that of the left partly, liquefied.

The right kidney weighed 320 gm.; the left, 330 gm. The capsules stripped easily revealing smooth, swollen surfaces. The cut section (Fig. 1) was firm, flat, pale tan, and unevenly marked by pin-point, dark red dots. The cortices were 5 to 7 mm. thick and the striations were hazy. The pyramids were uniformly enlarged and the striations were fairly distinct. The pelves and ureters were normal. The urinary bladder was empty and the lining was gray-red and wrinkled. The prostate, seminal vesicles, testes and epididymides were grossly not remarkable.

The ribs and vertebrae were hard and difficult to saw. The marrow of the ribs was light tan, soft, and abundant. The cranium was not examined.

Microscopic Examination

The tissues were fixed in 4 per cent formaldehyde, cut at 6 μ from paraffin, and stained with hematoxylin and eosin.

The thyroid showed large follicles well filled with colloid and lined by low cuboidal epithelium. The stroma contained a few small groups of lymphocytes. Calcium was deposited beneath the endothelium of many capillaries and in the intima of several small and medium arteries and veins.

Calcium was deposited in many muscle fibers of the heart (Fig. 2). It was most abundant in the muscle of the septum and left ventricle, moderately plentiful in the left auricle, sparse in the right ventricle, and absent from the right auricle. Subendothelial calcium deposits were observed in blood vessels of all sizes and the degree of deposition paralleled that seen in the myocardium of the four chambers. Much calcium was deposited in the endocardium of the left auricle, the appendage of which was stuffed by loosely adherent ante-mortem thrombus. In the aorta the intima was mildly thickened by lipoids, small groups of foamy macrophages, calcium, fibrous connective tissue, and hyalin. The other coats were intact.

The lungs revealed the following changes: diffuse hyperemia, edema fluid distending most alveolar ducts and alveoli, numerous alveolar phagocytes, dust macrophages in alveoli and in small groups in the stroma, and deposition of calcium (Fig. 3) in abundance beneath the endothelium of veins of all sizes, in many alveolar walls, in the submucosa of many bronchi and bronchioles, and in small amounts in the media of some arteries.

The spleen showed engorged sinusoids, recent sinusoidal hemorrhages, demarcated areas of coagulation necrosis, and calcium deposits in the intima of many large and small arteries and veins. The accessory spleens contained a few blood vessels with slight intimal calcium deposits.

In the upper half of the fundic mucosa of the stomach the glands were greatly autolyzed. The lower half showed extensive deposits of calcium in and around glandular crypts (Fig. 4) with involvement of both interstitial tissue and gland cells.

The parenchymal cells of the liver showed the finely foamy appearance of abundant glycogen. A few groups of liver cells contained coarse cytoplasmic fat vacuoles. The blood vessels were well preserved and contained no calcium. The periportal areas and the biliary ducts were intact. The perimuscular coat of the gallbladder revealed increased fibrous connective tissue and infiltrations of lymphocytes.

In the pancreas, calcium was deposited beneath the endothelium of blood vessels of all sizes, including interacinar and islet capillaries. Calcium was present also in the lamina propria of several medium and large ducts. An area of acinar tissue and fat tissue was partly liquefied and infiltrated by many segmented neutrophils and monocytes. Several groups of acini and some islets were autolyzed.

The adrenal glands displayed no significant histologic abnormalities.

In the kidneys (Fig. 5) numerous masses of calcium were found in all segments of the tubular system of the nephrons and were intermingled with sloughed calcified epithelial cells in the lumina of the tubules. Hyaline droplets distended many epithelial cells lining the convoluted tubules. Recently formed thrombi, some focally organized, plugged many medium and large veins. Many lymphocytes infiltrated the interstitial tissue. Calcium was deposited beneath the endothelium of some large arteries. Granules and masses of calcium were seen in the capsular fluid of some glomeruli and foreign body giant cells surrounded a few masses of calcium in the tubules. Hyaline casts filled many tubules and leukocytic casts distended others. A few glomeruli were obliterated by fibrosis, but most were well preserved.

The urinary bladder was not remarkable.

The prostate contained a few groups of moderately dilated acini. In the peripheral part of the stroma some large arteries exhibited deposits of subendothelial calcium. A few spermia were present in the tubules of the testes. The seminal epithelium was developed through the spermatid stage. An occasional tubule was obliterated by fibrous connective tissue.

A section of rib (Fig. 6) revealed a marrow-cell/fat-cell ratio of 75/25, fairly numerous megakaryocytes, a great increase in the myeloid/erythroid ratio, and a definite shift to the left in the neutrophilic granulocyte line. The cortical and medullary bone was involved by extensive ragged fraying and thinning of the bony trabeculae with countless osteoclasts nestling in the recesses along the scalloped edges of the bony trabeculae. Giemsa staining confirmed these findings.

The final anatomic diagnoses were as follows: Metastatic calcification, on the basis of hypervitaminosis D and haliphagia (ἅλς, *salt*, + φαγεῖν, to eat), involving the heart (chiefly of the endocardium and myocardium of the left auricle and ventricle), the lungs (pulmonary veins, alveolar walls, and bronchi), the fundic mucosa of the stomach, the kidneys, the pancreatic ducts, and the blood vessels of the thyroid gland, heart, spleen, pancreas, and prostate; calcific and hyaline droplet changes in the renal tubules with chronic interstitial inflammation and venous thrombosis; cardiac hypertrophy (480 gm.); mural thrombosis of the left auricle; pulmonary edema; acute passive congestion of viscera; recent infarcts in the spleen; osteoclastic resorption of bone; myeloid hyperplasia of bone marrow; acute focal pancreatitis; chronic cholecystitis and cholelithiasis; slight fatty metamorphosis of the liver; two accessory spleens; and absence of appendix, fibrous peritonitis, and healed laparotomy scar.

Qualitative Chemical Analysis of Lungs, Kidneys, and Gastric Mucosa

Fragments of lung (mainly alveoli in the periphery), kidneys (cortex and medulla), and fundic mucosa of the stomach were ground separately into a fine mush in a mortar. Microscopic examination of these tissues suspended in distilled water revealed amorphous material and fragmented cells but no crystals. When treated with a 50 per cent solution of hydrochloric acid, none of these tissues showed any macroscopic change. However, when 50 per cent sulfuric acid followed by 50 per cent hydrochloric acid was applied to the lung tissue, a grossly visible, violent evolution of gas bubbles was observed indicating the presence of a carbonate radical. The sulfuric acid evidently acted in some way to release calcium carbonate from the organic matrix of the lung, so that the hydrochloric acid was able to react with the carbonate

to produce carbon dioxide. This reaction was negative with the tissues from the kidney and gastric mucosa. When a 50 per cent solution of sulfuric acid was mixed with all three tissues, abundant formation of calcium sulfate crystals was seen histologically, thus demonstrating the presence of a calcium ion in all of them. When the kidney and gastric mucosa were treated with concentrated nitric acid and ammonium molybdate reagent and then heated, a yellow precipitate was formed indicating the presence of a phosphate radical in these tissues. With the same test the lung tissue was negative, for not only did no precipitate form, but the organic matter in the tissue was completely digested, so that a clear solution resulted. In summary, the qualitative chemical analysis of these organs showed that calcium phosphate was the salt deposited in the kidneys and gastric mucosa and that calcium carbonate was the salt deposited in the lungs.

Discussion

The case described is definitely an example of metastatic calcification as is easily proved by reference to the works of Askanazy,[1] Wells,[2] deSanto,[3] Grayzel and Lederer,[4] Wells and Holley,[5] and Herbert, Miller, and Richardson.[6] The heavy deposition of calcium in the endocardium and myocardium of the left chambers of the heart, in the pulmonary veins, bronchi, and alveolar walls, in the fundic mucosa of the stomach, in the kidneys, and in many arteries, capillaries, and even in veins, has been described by these authors. The places where acids are formed; namely, the lungs, the fundic mucosa of the stomach, and the kidneys, are organs in which the tissues are rendered alkaline when these acids are elaborated so that calcium deposition is favored.[2] The calcification of the endocardium and myocardium of the heart, of the arterial and capillary channels of the systemic circulation, and of the capillary and venous channels of the pulmonary circulation may also be explained on this basis, since the pH of the blood is higher in these tissues than in the venous side of the circulation, especially in the right chambers of the heart and in the pulmonary arteries. The ingestion by the patient of four inorganic salts containing sodium ions was a factor tending to increase tissue alkalinity. The deposition of calcium in the tissues was in the nature of a precipitation in previously healthy tissue cells and stroma, for the only degenerative change was the hyaline droplet alteration of the epithelial cells of the convoluted tubules of the kidneys and the only inflammatory infiltrations of significance were the interstitial infiltrations of lymphocytes and the leukocytic casts in some tubules of the same organs. This is in conformity with the original concept of Virchow,[18] who thought that the calcium

deposits in the stomach and lungs of his cases represented a direct calcification of the tissue by which lime salts penetrated and filled up the constituent parts of the organs involved.

Large doses of vitamin D in various forms have been employed to produce metastatic calcification in animals. Smith and Elvove [9] observed calcium deposits in the thoracic aorta, interalveolar septa, and kidneys of rabbits given irradiated ergosterol. Biochemical analysis revealed a progressive increase of serum calcium and the development of high inorganic phosphorus levels. In this study an elevated serum calcium and an increased serum phosphate level were necessary to produce appreciable tissue calcification, whereas with low or normal serum phosphorus values, calcium was not deposited in the tissues, even though the calcium of the blood was elevated. The authors thought that the salt concerned was calcium phosphate precipitated out in the tissues.

By giving viosterol to rats, Shelling [19] found that a greater susceptibility to hypercalcification of soft tissues resulted when the amount of phosphorus in the diet was increased.

With rats on an alkaline diet and large doses of oral calciferol, Gough, Duguid, and Davies [11] observed a heavy, quantitatively measured deposition of calcium in the kidneys, which was more pronounced than when the animals were on an acid diet. In excretion studies they found that the average urinary phosphorus was relatively low on an alkaline diet as compared to that on an acid diet. They also showed that phosphorus excretion was relatively decreased on both acid and alkaline diets by the calciferol.

In the experiments of Hess, Benjamin, and Gross,[20] the excessive administration of irradiated ergosterol caused a hypercalcemia in dogs fed a diet absolutely free of calcium. They thought that this excess calcium in the blood must come from the bones. The hypercalcemia was greatly reduced by the intravenous injection of sodium bicarbonate, after which a great excess of calcium and phosphorus was found in the lungs and kidneys and the calcium content of both urine and feces was definitely diminished. The histologic reaction in the bones of guinea-pigs given large doses of irradiated ergosterol was studied by Grauer,[21] who found in sections of costochondral junctions and long bones a resorption of bony trabeculae which were abundantly lined by osteoclasts, an increase in the size of the lacunar spaces, a thinning of the cortex, a proliferation of fibrous connective tissue in the marrow, and hemorrhage in the marrow cavities.

By applying the results of these experiments to the findings in the patient described, the vitamin D he ingested could have caused hyper-

calcemia,[9,20] phosphate retention,[9,11] and mobilization of calcium phosphate from the bones [20] as indicated by osteoclastic activity.[21] His diet was definitely alkaline through the ingestion of four sodium salts, which would favor the deposition of calcium salts in the soft tissues such as those of the kidneys.[11] An added source of phosphate further to augment the level of phosphate in the blood was available from the sodium phosphate taken by the patient. Finally, the sodium bicarbonate could have enhanced the calcium retention and favored an increase of calcium and phosphorus in such organs as the lungs and kidneys.[21]

No obvious tumors were observed near the thyroid gland. The absence of osteitis fibrosa cystica militated against the presence of a neoplasm in an aberrant parathyroid gland. The changes in the kidneys of patients with primary hyperparathyroidism have been described by Anderson.[22] The characteristic features include the following: interstitial fibrosis, interstitial, *mainly peritubular*, calcification, interstitial infiltrations of lymphocytes and plasma cells, cystic dilatation of tubules, thickening and sometimes calcification of the basement membranes of tubules, a relative absence of active glomerulitis or involvement of the epithelial cells of the tubules, sometimes formation of calculi and superimposed ascending infection, and obstruction and dilatation of tubules by the peritubular calcium deposits. Not only do these microscopic changes differ strikingly from the histologic features for the kidneys in my case, but the weight of the kidneys in the cases described by Anderson [22] was far below the tremendous weight (650 gm., combined) of the kidneys in the case reported. Both the gross and microscopic findings in the kidneys of the hitherto reported human cases of hypervitaminosis D [14-17] are much more nearly comparable to those in my case.

The mural thrombosis of the left auricle and the thrombosis of the renal veins were possibly on the basis of a high tissue alkalinity associated with a high content of calcium ions in the blood in these locations to hasten the clotting reactions. Askanazy's [1] first case of widespread involvement of the skeletal system by malignant melanoma and hemorrhagic nephritis also showed thrombosis of the renal veins. The cardiac hypertrophy may be explained on the basis of enlargement of uncalcified muscle fibers to compensate for those involved by calcium deposits. The recent infarcts of the spleen could have been caused by lodgment of emboli from the mural thrombus in the left auricle, although these emboli were not actually demonstrated. The deposition of calcium in the lamina propria of the pancreatic ducts has not hitherto been de-

scribed in cases of metastatic calcification. No explanation is obvious for the myeloid hyperplasia of the bone marrow.

SUMMARY

Widespread metastatic calcification involving the heart, lungs, gastric mucosa, kidneys, pancreas, and numerous blood vessels of a male patient, 44 years of age, was associated with the ingestion of vitamin D and alkaline inorganic salts. The reasons for this extensive direct calcification of soft tissues in all probability included hypercalcemia, phosphate retention, mobilization of calcium phosphate from the bones brought about by osteoclastic activity, a high alkaline diet, an excess of ingested phosphate, and the enhancement of calcium retention by the intake of sodium bicarbonate. Qualitative chemical analysis demonstrated the presence of calcium carbonate in the lungs and of calcium phosphate in the gastric mucosa and kidneys.

Since this paper was submitted for publication, a case of metastatic calcification in a woman, 32 years old, has been reported by J. M. Bauer and R. H. Freyberg (Vitamin D intoxication with metastatic calcification. *J. A. M. A.*, 1946, **130**, 1208–1215). This woman received large amounts of irradiated ergosterol, largely calciferol, for 1 year before death. At autopsy calcification of the kidneys, right knee joint, myocardium, endocardium of the left auricle, systemic arteries, lungs, dura, and subcutaneous tissue of the left ischial region was found. Also present were a chronic fibrous pneumonitis and a chronic duodenal ulcer.

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[*Illustrations follow*]

DESCRIPTION OF PLATE

PLATE 269

FIG. 1. Kidney, cut section. About ½ ×.

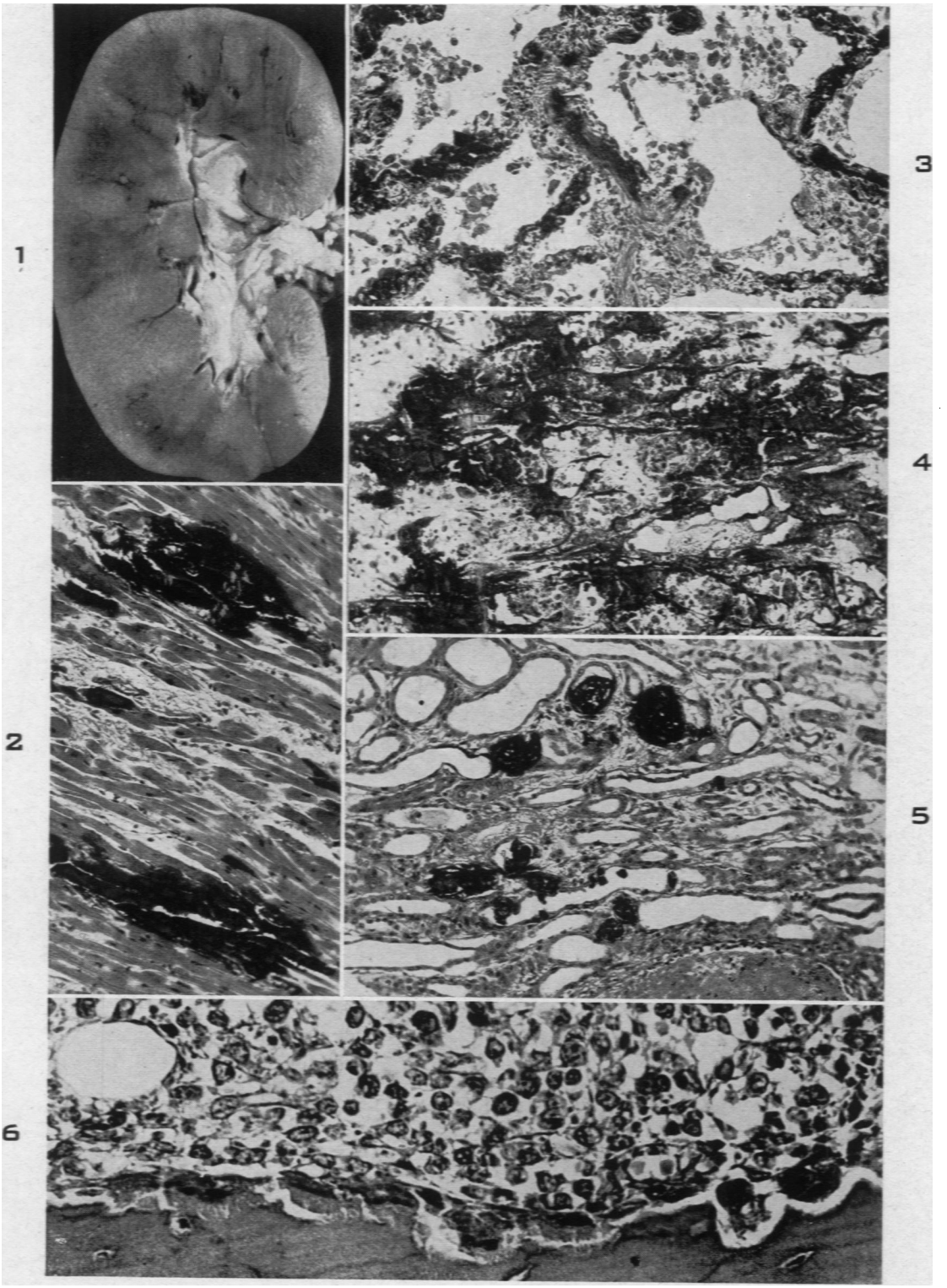
FIG. 2. Myocardium of left ventricle, showing groups of calcified muscle fibers. × 130.

FIG. 3. Lung, showing calcium deposits in walls of alveoli. × 130.

FIG. 4. Gastric mucosa with calcium deposits in gland cells and interstitial tissue. × 135.

FIG. 5. Kidney, showing calcium masses in lumina of tubules, several with calcified cells. Of note is the renal vein in the lower right-hand corner, containing a thrombus. × 130.

FIG. 6. Rib with osteoclasts lining a ragged bony trabecula below, and cellular marrow above. × 365.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